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## Hippocampal atrophy on MRI from aging to dementia

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2007

### **document version**

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### **citation for published version (APA)**

van de Pol, L. A. (2007). *Hippocampal atrophy on MRI from aging to dementia: a clinical perspective*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

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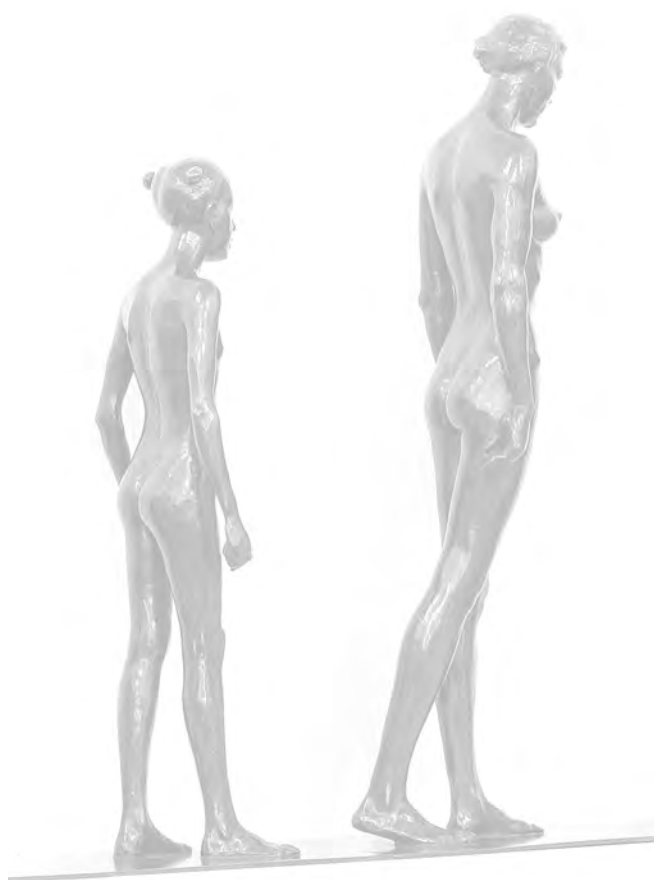
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## **Aims of this thesis**



## CHAPTER 2

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## AIMS OF THE THESIS

In the introduction an overview was given of the current use of hippocampal atrophy measured using MRI in the context of AD and MCI. The general objective of this thesis was to explore further hippocampal atrophy using MRI in the spectrum from normal aging to dementia. Three specific topics were addressed:

### 1. THE ROLE OF HIPPOCAMPAL ATROPHY IN THE DIAGNOSIS OF ALZHEIMER'S DISEASE

First, we investigated the limits of the use of hippocampal atrophy as a diagnostic marker for AD. Most studies assessing the diagnostic value of hippocampal atrophy for AD have compared typical, elderly patients with AD to healthy controls. Little is known about whether hippocampal atrophy is relevant in the diagnosis of AD either in young, or in very old subjects. In **chapter 3.1**, we aimed to dissect the effects of aging and AD on hippocampal atrophy. If the difference in hippocampal volumes between patients with AD and healthy controls could be shown to be modified by age, this would have implications for the diagnostic value of hippocampal atrophy in specific age-categories. For this purpose, hippocampal volumes of patients with AD and controls in a wide age-range (51-85 years) were examined. Furthermore, hippocampal atrophy may not be specific for AD, which may complicate the differential diagnosis between AD and other neurodegenerative disorders, such as FTLD. In **chapter 3.2**, the results of a study investigating hippocampal atrophy in FTLD in comparison to AD are presented. Hippocampal volumes and MTA scores were compared between subjects with FTLD, AD and controls and subsequently between the three clinical subtypes of FTLD: frontotemporal dementia, semantic dementia and progressive non-fluent aphasia. If hippocampal atrophy would be observed in FTLD, this would add to existing evidence that hippocampal atrophy is not restricted to AD. We also investigated the differences in severity or symmetry of hippocampal atrophy between (subtypes) of FTLD and AD. This is particularly relevant in view of the differential diagnosis between AD and FTLD, which can be difficult in clinical practice.

### 2. MRI CHARACTERISTICS OF MILD COGNITIVE IMPAIRMENT

Second, we addressed the role of hippocampal atrophy in the early stages of disease, before a diagnosis of dementia can be made. As discussed, about 15% of subjects with MCI will develop AD each year, whilst others will develop different types of dementia, remain cognitively stable or even improve over time. A better means of identifying the

underlying aetiologies of MCI, and its clinical subtypes, is needed to improve accurate identification of those at risk of developing AD. We investigated the prevalence of MRI abnormalities suggestive of Alzheimer-type and microvascular pathology and their clinical associations in two large cohorts of subjects with MCI. In **chapter 4.1** we describe the severity of MTA and small vessel disease, rated as WMH and the presence of lacunes, in a large cohort of subjects with MCI. We investigated the associations between these MRI characteristics and measures of cognition: general cognition, episodic memory and performance on the digit symbol substitution test. Parallel with the clinical heterogeneity, we expected to find a wide range in severity of MTA and small vessel disease within the MCI cohort, and hypothesized that evidence for MTA and small vessel disease would each be associated with specific cognitive measures. In **chapter 4.2**, we compared the severity of MTA and WMH in four clinical MCI subtypes, based on their neuropsychological test performance: subjective complaints, non-amnestic MCI, single-domain amnestic MCI, and multiple-domain amnestic MCI. If certain MRI profiles could be shown to be associated with specific MCI subtypes, this would improve insight in associated brain changes and provide clues to the final clinical outcome of the MCI subtypes.

### 3. LONGITUDINAL STUDIES: RATES OF HIPPOCAMPAL ATROPHY

Third, a longitudinal perspective was taken as we focused on rates of hippocampal atrophy. Rates of hippocampal atrophy have been suggested to be more sensitive diagnostic markers of AD than hippocampal volumes, and provide a means of tracking disease progression. Studies identifying risk factors for the progression of hippocampal atrophy are lacking. Therefore in **chapter 5.1**, we aimed to identify baseline risk factors, in subjects with MCI, leading to accelerated rates of hippocampal atrophy, itself suggestive of the accumulation of Alzheimer-type pathology which may become clinically manifest in the future. We measured rates of hippocampal atrophy from serially acquired MRI scans, in a large cohort of subjects with MCI. We investigated possible risk factors for progression of hippocampal atrophy, which in turn would reflect clinical progression. This may be relevant in terms of possible therapeutic options and enrichment of future trial cohorts. Finally, a methodological study was performed; in **chapter 5.2** we describe the results of a study in which we investigated a novel semi-automated technique for measuring progression of hippocampal atrophy. We compared the agreement and reliability of regional non-linear (fluid) registration versus manual delineation for measuring rates of hippocampal atrophy in a cohort of MCI subjects.

In **chapter 6**, the main findings of this thesis are discussed with reference to the literature, and implications and recommendations for future research are outlined.